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#### UNITED STATES PATENT AND TRADEMARK OFFICE

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# BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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Ex parte JAMES T. ENGLISH, FRANCIS J. SCHMIDT, GEORGE P. SMITH, ROY O. MORRIS, and SHARON BISHOP-HURLEY

Appeal 2008-2259 Application 09/829,549 Technology Center 1600

Decided: June 16, 2008

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Before TONI R. SCHEINER, DONALD E. ADAMS, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

ADAMS, Administrative Patent Judge.

#### **DECISION ON APPEAL**

This appeal under 35 U.S.C. § 134 involves claims 1-9 and 32-51, the only claims pending in this application. We have jurisdiction under 35 U.S.C. § 6(b).

#### INTRODUCTION

The claims are directed to a method for identification of non-immunoglobulin peptides having an affinity for the surface of a fungus. Claim 1 is illustrative:

- 1. A method for identification of non-immunoglobulin peptides having an affinity for the surface of a fungus comprising:
  - (a) constructing a library of peptides by,
    - (i) preparing random oligonucleotides:
- (ii) inserting said oligonucleotides into a vector that expresses peptides encoded by said random oligonucleotides on its surface and is capable of transfecting a host cell;
- (iii) transfecting a host cell with said vector to amplify said vector in an infectious form to create a library of peptides on the surface of said vector;
- (b) contacting said vector expressing said peptide library with a target fungus and removing unbound vector;
  - (c) eluting bound vector from said fungus;
  - (d) amplifying said bound vector;
  - (e) sequencing the oligonucleotides contained in said eluted vector;
- (f) deducing the amino acid sequence of peptides encoded by said oligonucleotides contained in said eluted vector; and
- (g) selecting the non-immunoglobulin peptides for which the amino acid sequence has been deduced.

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The Examiner relies on the following prior art references to show unpatentability:

Qiu et al. US 6,235,974 B1 May 22, 2001 Kodadek US 2001/0029024 A1 Oct. 11, 2001

V.A. Petrenko et al., *A library of organic landscapes on filamentous phage*, 9 Protein Engineering no. 9, 797-801 (1996).

George P. Smith et al., *Libraries of Peptides and Proteins Displayed on Filamentous Phage*, 217 Methods in Enzymology 228-257 (1993).

Kevin C. Gough et al., Selection of phage antibodies to surface epitopes of Phytophthora infestans, 79 J. Immunological Methods 97-108 (1999).

The rejections as presented by the Examiner are as follows:

- 1. Claims 1-4, 6-9, 32-34, 37-43, 45-47, and 49-51 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Gough, Kodadek and Petrenko.
- 2. Claims 44 and 49 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Gough, Kodadek and Petrenko.
- 3. Claim 5 stands rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Gough, Kodadek, Petrenko, and Smith.
- 4. Claims 35, 36, and 48 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Gough, Kodadek, Petrenko, and Qui. We affirm.

### **DISCUSSION**

## *Findings of Fact* (FF):

- 1. Gough teaches "[a] phage library displaying scFv antibody fragments on protein III of bacteriophage M13 . . . was used to isolate binders to the surface epitopes of *P. infestans* germlings (Gough 101, col. 2, ll. 4-7).
- 2. *P. infestans* is a fungal plant pathogen (Gough 97, col. 2, 1. 2 98: col. 1, 1. 10; Ans. 4).
- 3. Gough's phage display library "has a repertoire of over 10<sup>10</sup> antibody fragments" (Gough 98, col. 2, 11. 5-7).
- 4. Gough teaches that *P. infestans* germlings or soluble external components of *P. infetans* were contacted with the phage display library, unbound phage were removed, bound phage were eluted, and used to infect host cells for amplification (Gough 99, col. 1. 2 col. 2, 1. 40; Ans. 3-4).
- 5. Gough teaches that "[t]he use of such methods to isolate antibodies to native biologically relevant, surface-exposed, epitopes may lead to the production of immunological probes to identify specific cell components and determine their distribution and function" (Gough 98, col. 2, ll. 12-17).
- 6. Gough does not disclose non-immunoglobulin peptides or a f8-1 peptide library (Ans. 4).

7. Kodadek teaches that antibodies are

proteins; not low molecular weight compounds. They are relatively fragile compared to small molecules. Using classical methods, they are tedious and expensive to obtain, particularly in large quantities, although advances in the construction of single chain antibody libraries on phage . . . promise to speed up this process. Finally, antibodies are not easily rendered cell-

(Kodadek ¶ 0009; Ans. 4.)

permeable.

- 8. Kodadek's goal "was to develop a general method for the discovery of relatively low molecular weight EBMs [(epitope-binding molecules)] that can be chemically synthesized (i.e., they are not macromolecules such as antibodies, other types of proteins, or nucleic acids)" (Kodadek ¶ 0038).
- 9. Kodadek teaches the production of peptide libraries constructed by, *inter alia*, the production of random oligonucleotides and ligation into a "library vector" (Kodadek ¶ 0061). Kodadek refers to this peptide library as pincer library (Kodadek ¶ 0132).
- 10. Kodadek teaches a library wherein peptides are displayed on the surface of a bacteriophage (Kodadek ¶ 0132).
- 11. Kodadek teaches that "[f]or screening the phage-displayed . . . libraries, a standard panning protocol will be employed . . ." (Kodadek ¶ 0136).
- 12. Kodadek teaches that "[t]he identity of the phage-displayed peptide encoded by the library . . . will be determined by DNA sequencing of DNA isolated from the phage" (*id*.).
- 13. Pentrenko teaches that "[p]hage tolerate the fusion of foreign peptides to the N-terminus of pVIII . . . and the surface architecture of virions with these altered coat proteins can be substantially altered . . . implying that the peptide interacts with the surrounding virion surface to form a well-defined structure. Such recombinant phage are reminiscent of antibody molecules" (Petrenko 797, col. 1, 11. 9-16).
- 14. Petrenko's "library was constructed by replacing wild-type amino acids 2-4 with random octamers on every pVIII subunit . . .; the octamers are arranged regularly around the outside of the virion, occupying a substantial

fraction of the surface area" (Petrenko 799, col. 2, ll. 5-9). Petrenko refers to this library as a landscape phage library (Pentrenko 797, col. 1, ll. 28-29).

- 15. Petrenko "report the construction of a  $1.5 \times 10^9$ —clone landscape library, and the use of simple microbiological methods to select clones exhibiting both local properties (specific affinity for a small organic hapten, mimicry of antigenic epitopes) and a global one (resistance to chloroform)" (Petrenko 797 col. 1, 1. 29 col. 2, 1. 2).
- 16. Petrenko teaches the use of the f8-1 vector (Petrenko 797, Fig. 1 legend; 798, col. 1, l. 11 col. 2, l. 8; Ans. 4).
- 17. Petrenko teaches that "landscape phage are not designed and synthesized one by one with particular goals in mind. Instead, phage with particular attributes are selected from huge libraries with random surface architectures" (Petrenko 800, col. 2, ll. 29-32).
- 18. Petrenko teaches "landscape phage as alternative 'antibodies'" and exemplifies clones from the landscape phage library that bind dioxin (Petrenko 800, col. 1, ll. 3-24).
- 19. Petrenko teaches that phage clones and target were contacted, unbound phage were removed, bound phage were eluted, and used to infect host cells for amplification (Petrenko 798, col. 2, ll. 10-27).
- 20. Petrenko teaches a random oligonucleotide sequence comprising the sequence "GCA Gnk (nnk)<sub>6</sub> nnG" (Petrenko 797, Fig. 1 and legend). Pentrenko teaches that "n represents an equal mixture of G, A, T and C, and K an equal mixture of G and T" (*id.*).
- 21. Smith teaches libraries of peptides and proteins displayed on filamentous phage (Smith 228, Title).

- 22. Smith teaches that phage displaying peptides on their surface are particularly well suited for the construction of epitope libraries (Smith 228:2-6).
- 23. Smith teaches that phage display libraries "display 'random' foreign peptides encoded by degenerate synthetic oligonucleotides spliced into the coat protein gene, the library as a whole representing up to billions of peptide sequences" (Smith 228:6-10).

### 24. Smith teaches that

[m]ost libraries to date have used synthetic degenerate oligonucleotides as the insert. A degenerate oligonucleotide is a mixture of sequences created in a single synthesis by coupling mixtures of nucleotides, rather than single nucleotides, at selected positions in the growing chain. At the codon level degeneracy can be of two general types: fully degenerate codons encode all 20 amino acids with no bias beyond what is entailed by the unequal degeneracy of the genetic code; while doped codons are biased toward one particular amino acid in order to introduce random substitutions into a base peptide or polypeptide sequence.

(Smith 243:13-21).

25. Qui teaches that a number of fungi were known in the art prior to Appellants' filing date, including the *Phytophthora* species capsici, cinnamoni, and parasitica (Qui 22:20-21).

# Analysis:

1. Claims 1-4, 6-9, 32-34, 37-43, 45-47, and 49-51 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Gough, Kodadek and Petrenko.

Based on the evidence relied upon the Examiner concludes that

"[i]t would have been obvious to one having ordinary skill in the art at the time the invention was made to substitute a [sic] small molecular weight compounds as peptides in the method of Gough as taught by Kodadek and Petrenko" (Ans. 4).

In response, Appellants provide separate arguments for the following two claim groupings: I. claims 1-4, 6-8, 32-34, 37-40, 45-47, and 49-51; and II. claims 9 and 41-43. Therefore, we limit our discussion to representative claims 1 and 42. 37 C.F.R. § 41.37(c)(1)(vii).

## Claim 1:

According to Appellants, since Gough teaches "a library of scFv antibody fragments" Gough does not "teach or suggest the selection of non-immunoglobulin peptides that bind epitopes on the surface of a fungus" (App. Br. 9 (emphasis removed)). In this regard, Appellants point out that their Specification defines a "non-immunoglobulin peptide" to mean "a peptide which is not an immunoglobulin, a recognized region of an immunoglobulin, or contains a region of an immunoglobulin. For example, a single chain variable region of an immunoglobulin would be excluded from this definition" (App. Br. 9, n. 36; Spec. 9: 16-19). We are not persuaded by this argument which fails to account for the teachings of Kodadek and Petrenko.

We agree with Appellants that Gough is interested in isolating "antibodies to native biologically relevant, surface-exposed, epitopes [which] may lead to the production of immunological probes to identify specific cell components and determine their distribution and function" (FF 5; App. Br. 9-10). We disagree, however, with Appellants' intimation that the substitution of random peptide libraries for Gough's phage display

library would *not* have been obvious in view of the combination of references relied upon (App. Br. 9-10).

As Appellants appreciate, Gough "describe[s] methods for the isolation of antibodies specific for surface-exposed epitopes on certain species of *Phytophthora*" (App. Br. 8 (emphasis removed); FF 1). Petrenko teaches a 1.5 x 10<sup>9</sup>—clone landscape phage library, teaches "landscape phage as alternative 'antibodies'", and exemplifies clones from the landscape phage library that bind dioxin (FF 15 and 18). Kodadek teaches phage-displayed pincer libraries that bind to an epitope target (FF 7-10). We find no limitation in Appellants' claimed invention that would exclude the use of either a landscape phage library as taught by Petrenko or a phage-displayed pincer library as taught by Kodadek. There is no evidence on this record that a person of ordinary skill in the art at the time this invention as made¹ would not have appreciated that a clone selected through the use of Gough's methodology from the library of either Petrenko or Kodadek would not be useful as a probe to identify specific cell components and determine their distribution and function as taught by Gough.

Because claim 1 does not require that the selected peptides exhibit anti-fungal activity, we are also not persuaded by Appellants' assertion that Gough's "approach did not work" because "it 'showed no detectable anti-fungal activity for any of the antibodies'" (App. Br. 10; *see also* App. Br. 17).

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Obviousness is determined in terms of the level of skill of a person having ordinary skill in the art at the time the invention was made. 35 U.S.C. § 103; *Graham v. John Deere Co.*, 383 U.S. 1 (1966).

Claim 1 requires that the selected peptides have affinity for the surface of a fungus. As Appellants recognize Gough's method was "effective in identifying antibodies that bind to the surface of *Phytophthora*" (App. Br. 9). For the reasons set forth above we find that a person of ordinary skill in this art, following the teachings of the combination of references relied upon by the Examiner, would have been led to a method for identifying non-immunoglobulin peptides having an affinity for the surface of a fungus.

Appellants' note that Kodadek teaches "early efforts by Kodadek and co-workers to isolate small peptides using phage display methods 'failed completely" (App. Br. 13 (emphasis removed); Kodadek ¶ 0038). From this Appellants assert that Kodadek teaches away from the use of phage display methods; that Kodadek teaches that "random peptides . . . are inadequate for his purpose"; and that "Kodadek and Gough et al. represent mutually exclusive domains, and, therefore, any suggestion of substitution of the peptides of Kodadek into the methods of Gough et al. would not be feasible" (App. Br. 12-13 (emphasis removed)). Because Appellants have taken Kodadek's statement out of context, we are not persuaded by Appellants' assertions.

Kodadek was interested in isolating "heteromeric complexes comprised of small peptides, even smaller than lucine zippers, that could be employed as EBMs" (Kodadek ¶ 0038). Kodadek reports, however, that due to the size of the molecules "it was not clear how feasible this endeavor would be" (id.). In this regard, Kodadek reports that early attempts to isolate heteromeric complexes comprised of small peptides that could be employed as EBMs were not successful (id.). This, however, is not the end of the

story. Kodadek teaches that "the inventor has now demonstrated that it is indeed feasible to isolate highly specific complexes between relatively small peptides" (Kodadek ¶ 0039). Kodadek In this regard, Kodadek teaches, as one embodiment, phage displayed pincer libraries that are used to identify phage clones containing EBMs "that bind to an immobilized epitope target" (Kodadek ¶ 0132). Accordingly, we are not persuaded by Appellants' emphasis on Kodadek's early efforts. There is no evidence on this record to suggest that the substitution of Kodadek's randomized peptide phage display library into Gough's method would not result in a productive method of identifying peptides having affinity for the surface of a fungus.

Further, such a position would be inconsistent with Petrenko who teaches "landscape phage as alternative 'antibodies'" and exemplifies clones from the landscape phage library that bind dioxin (FF 18). In this regard, we are not persuaded by Appellants' arguments directed at Petrenko.

According to Appellants, Petrenko teaches "panning phage displayed peptides against . . . a single known target seeking to identify phage clones that exhibit 'global properties' across the entire phage surface" (App. Br. 15 (emphasis removed)). From this Appellants assert that since Gough's "target was a multitude of unknown surface epitopes presented on the surface of *Phytophthora*" and Gough was "seeking to identify specific antibodies that bind to the surface of *Phytophthora*," one would not be motivated to modify Gough with Petrenko. We are not persuaded.

To the extent that Appellants would suggest that the presence of more than one target, or unknown target(s), will confound the phage in the library and lead to the failure of a binding event, we disagree. The presence of a number of targets would reasonably be expected to enhance the binding

opportunities of the phage in the library. There is no evidence on this record to suggest otherwise. As Petrenko explains, "landscape phage are not designed and synthesized one by one with particular goals in mind. Instead, phage with particular attributes are selected from huge libraries with random surface architectures" (FF 17). In this regard, Petrenko teaches "landscape phage as alternative 'antibodies'" and exemplifies a clones from the landscape phage library that bind dioxin (FF 18).

We are also not persuaded by Appellants' assertion that "[i]t is not enough that the peptide libraries, or specifically Petrenko et al.'s f8-1 peptide library, could be theoretically substituted into the methods of Gough" (App. Br. 16). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007). For the reasons set forth above, we find that a person of ordinary skill in this art would have reasonably expected to successfully identify peptides which have affinity for a fungus using the method taught by the combination of references relied upon.

On reflection, we find that the Examiner has provided the evidence necessary to establish a prima facie case of obviousness. Accordingly, the burden of coming forward with evidence or argument was properly shifted to Appellants. *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993). For the foregoing reasons, Appellants have failed to carry their burden.

Accordingly, we affirm the rejection of claim 1 under 35 U.S.C § 103(a) as unpatentable over the combination of Gough, Kodadek and Petrenko. Claims 2-4, 6-8, 32-34, 37-40, 45-47, and 49-51 fall together with claim 1.

### *Claim 42*:

Claim 42 depends from, *inter alia*, claim 1 and further limits the peptide library to an f8-1 peptide library. As claim 42 does not require any particular peptide length we are not persuaded by Appellants' arguments regarding peptide length (App. Br. 18-20). Further, we are not persuaded by Appellants' assertion that one would not have been motivated to utilize a f8-1 phage library as taught by Petrenko because Gough's "method 'showed no detectable antifungal activity for any of the antibodies'" (App. Br. 20). Claim 42 does not require that the selected peptide exhibit antifungal activity. Further, for the reasons discussed above, we are not persuaded by Appellants' assertion that "Kodadek said it would not work" (*id.*).

On reflection, we find that the Examiner has provided the evidence necessary to establish a prima facie case of obviousness. Accordingly, the burden of coming forward with evidence or argument was properly shifted to Appellants. *Rijckaert*, 9 F.3d at 1532. For the foregoing reasons, Appellants have failed to carry their burden. Accordingly, we affirm the rejection of claim 42 under 35 U.S.C § 103(a) as unpatentable over the combination of Gough, Kodadek, and Petrenko. Claims 9, 41, and 43 fall together with claim 42.

2. Claims 44 and 49 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Gough, Kodadek and Petrenko.

The claims have not been argued separately and, therefore, stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Therefore, we limit our discussion to representative claim 44. Claim 44 depends from, *inter alia*, claim 1 and further limits the peptide library to an f88-4 peptide library.

The Examiner relies on the combination of Gough, Kodadek, and Petrenko as discussed above. Gough, Kodadek, and Petrenko do not teach an f88-4 peptide library. To make up for this deficiency, the Examiner relies on Appellants' Specification (Spec. 11:28 - 12:2) to teach that "methods for the production of the f88-4 phage-displayed peptide library have . . . been previously described [(Zhong et al., *J. Biol. Chem.* 269:24183-24188, 1994; Smith and Scott, *Methods in Enzymology*, 217:228-257, 1993; Smith, *Gene*, 128:1-2, 1993 and references cited therein)]" (Ans. 5).

Based on this evidence the Examiner finds that it would have been prima facie obvious to a person of ordinary skill in the art to have utilized the f88-4 library in the method taught by the combination of Gough, Kodadek, and Petrenko (*id.*). Appellants admit that "[a]t the time of Appellants' invention, random peptide libraries in general were known in the art, and included such random peptide libraries as the f8-1 and the f88-4 phage-displayed peptide libraries" (App. Br. 20). Accordingly, we find no error in the Examiner's prima facie case of obviousness.

Appellants assert that while the references they cite to teach f88-4 peptide libraries predate Gough by "at least three years" Gough "still selected a phage-antibody library of scFv fragments" (App. Br. 21 (emphasis removed)). We are not persuaded. Gough teaches the use of phage libraries to identify molecules (scFv fragments) that have affinity for *Phytophthora*. In addition, the evidence relied upon by the Examiner teaches the methodology for the identification of molecules (peptides) that have affinity for target molecules (FF 1-19) and the use of f88-4 phage. Contrary to Appellants' intimation, Gough's interest in scFv phage libraries does not shut the door on the use of other phage libraries (e.g., those taught by

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Kodadek and Petrenko) to identify molecules that have affinity for the surface of a fungus.

For the foregoing reasons, we find no error in the Examiner's conclusion that it would have been prima facie obvious to have utilized f88-4 peptide libraries in the method taught by the combination of evidence relied upon to identify peptides having affinity for the surface of a fungus.

As claim 44 does not require antifungal activity, we are not persuaded by Appellants' arguments based on antifungal activity (App. Br. 21).

For the foregoing reasons, we affirm the rejection of claim 44 under 35 U.S.C § 103(a) as unpatentable over the combination of Gough, Kodadek, and Petrenko. Claim 49 falls together with claim 44.

3. Claim 5 stands rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Gough, Kodadek, Petrenko, and Smith.

Claim 5 depends from, *inter alia*, claim 1 and further limits the sequence of the random oligonucleotide to GCA GNN (NNN)7 or SEQ ID NO: 1.

The Examiner relies on the combination of Gough, Kodadek, and Petrenko as discussed above. In addition, the Examiner finds that Petrenko teaches a random oligonucleotide sequence comprising the sequence GCA Gnk (nnk)<sub>6</sub> nnG "as opposed to the claimed GCA GNN (NNN)7" (Ans. 7; FF 20). To make up for this deficiency the Examiner relies on Smith to teach the use of phage libraries with fully degenerate oligonucleotide inserts (Ans. 6; FF 23).

Based on this evidence the Examiner concludes that "it would have been obvious to one having ordinary skill in the art at the time the invention was made to use" phage libraries with fully degenerate oligonucleotide inserts in the method taught by the combination of Gough, Kodadek, and Petrenko.

In response, Appellants assert that Smith provides no suggestion or motivation to utilize degenerate oligonucleotides in the method of Gough, and that there is no reason to believe that the substitution of random peptide libraries formed using degenerate oligonucleotides would even work. We disagree. The combination of Gough, Kodadek, and Petrenko teach a method wherein randomized peptide phage display libraries are used to identify a peptide having affinity for the surface of a fungus. Every one of these references teaches a phage display library in which at least one peptide (which includes scFV) has some affinity for a target. There is no reason to expect that a phage library comprising fully degenerate oligonucleotides would not contain at least one peptide that exhibits some level of affinity for the surface of a fungus. Further, there is no evidence on this record which would support a contrary conclusion. Therefore, we are not persuaded by Appellants' assertion to the contrary.

Accordingly, we affirm the rejection of claim 5 under 35 U.S.C § 103(a) as unpatentable over the combination of Gough, Kodadek, Petrenko, and Smith.

4. Claims 35, 36, and 48 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Gough, Kodadek, Petrenko, and Qui.

The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Therefore, we limit our discussion to representative claim 35. Claim 35 depends from, *inter alia*, claim 1 and

further limits the target fungus to one selected from the group consisting of *Phytophthora sojae, Phytophthora capsica, Phytophthora palmivora, Phytophthora cinnamomi,* and *Phytophthora parasitica.* 

The Examiner relies on the combination of Gough, Kodadek, and Petrenko as discussed above, but recognizes that this combination of references does not specifically disclose the *Phytophthora* species recited in claim 35 (Ans. 7). To make up for this deficiency the Examiner relies on Qui to teach "the different species of Phytophthora . . . are known in the art at the time of the invention" (*id.*).

Based on this evidence the Examiner concludes that it would have been obvious to one having ordinary skill in the art to use other phytophthora species in the method taught by the combination of references relied upon (Ans. 7-8).

In response Appellants acknowledge that a number of *Phytophthora* species were known in the art prior to their filing date (App. Br. 23). Nevertheless, Appellants assert that Qui does not suggest that any of the fungi would be desirable in the methods of Gough (App. Br. 24). We are not persuaded. The combination is not Qui and Gough. To the contrary, the Examiner relies on the combination of Gough, Kodadek, Petrenko, and Qui. For the foregoing reasons, we find no error in the Examiner's prima facie case of obviousness. We find no evidence or persuasive argument that a person of ordinary skill in the art would not recognize that peptides having affinity for the surface of any number of fungi, including the *Phytophthora* species *capsici*, *cinnamoni*, and *parasitica* could have been identified using the methodology taught by the combination of references relied upon.

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Further, there is no evidence on this record that one of ordinary skill in the art would not have been able to identify peptides that bind the surface of any one of the fungi taught by Qui that would be useful as probes to identify specific cell components and determine their distribution and function as taught by Gough (FF 5).

Accordingly, we are not persuaded by Appellants' arguments.

For the foregoing reasons, we affirm the rejection of claim 35 under 35 U.S.C § 103(a) as unpatentable over the combination of Gough, Kodadek, Petrenko, and Qui. Claims 36 and 48 fall together with claim 35.

## **CONCLUSION**

In summary, we affirm the rejections of record.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

# **AFFIRMED**

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SENNIGER POWERS LLP ONE METROPOLITAN SQUARE 16TH FLOOR ST. LOUIS, MO 63102